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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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08/978,636

11/25/1997

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Enz-53(D3)

4642

28171

7590

06/09/2011

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EXAMINER

BOWMAN, AMY HUDSON

ART UNIT

PAPER NUMBER

1635

MAIL DATE

DELIVERY MODE

06/09/2011

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 08/978,636	<b>Applicant(s)</b> RABBBANI ET AL.	
	<b>Examiner</b> AMY BOWMAN	<b>Art Unit</b> 1635	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 4/4/11.
- 2a) ☒ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 245, 247-255, 262, 265 and 268-271 is/are pending in the application.
- 4a) Of the above claim(s) 268 and 269 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 245, 247-255, 262, 265, 270, and 271 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 November 2007 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____.   | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of Application/Amendment/Claims***

Applicant's response filed 4/4/11 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 10/4/10 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/4/11 has been entered.

Claims 245, 247-255, 262, 265, and 268-271 are pending in the instant application.

This application contains claims 268 and 269 that are drawn to an invention nonelected with traverse in the reply filed on 10/9/07 and are therefore withdrawn.

***Response to Applicants Arguments-- 35 USC § 112***

Claims 245, 247-255, 262, 265, 270, and 271 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. This rejection is repeated for the same reasons of record as set forth in the actions mailed 5/31/05, 6/27/06, 4/4/07, 12/26/07, 9/15/08, 6/22/09, and 1/26/10.

Although applicant asserts that it was known in the art how to insert introns in a predictable fashion, there is not sufficient description for choosing the location of insertion of the intron sequences within the context of the instant invention, as it is not evident that insertion of any intron into any sequence encoding any intron, especially wherein the insertion is at any position, would result in the instantly recited outcomes. The instant claims are not closed to introns with any specific structural characteristic that would narrow the genus to those introns that are predictably spliced in eukaryotes.

Applicant asserts that methods are well known in the art for introducing artificial introns. It is not disputed that methods are known in the art to introduce artificial introns. However, it is the unpredictable nature of introducing any intron into any nucleic acid sequence at any position that encodes any polymerase with a resultant incapability of the polymerase being expressed in any prokaryotic cell, whereas more than one copy of a nucleic acid sequence is produced when introduced into any eukaryotic cell. Furthermore, the claims recite that the gene product or protein expressed would be lethal specifically to a prokaryotic cell in the absence of the intron.

Applicant points to example 19, which is directed to a eukaryotic vector that expresses T7 RNA polymerase as well as antisense sequences directed by a T7

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promoter. The example sets forth a specific SV40 small T intron that has stop codons in three reading frames and wherein there are 19 different sites with the T7 RNA polymerase coding sequence that contain the sequence (C/A)AGG, which is a consensus sequence for a post-splice junction. None of these are elements in combination are required by the instant claims.

Applicant points to Schwartz, Mayeda and Gattermann for teachings of specific instances where introns have been inserted and spliced in eukaryotic cells and not in prokaryotic cells. It is acknowledged that insertion of an intron into a coding sequence may result in splicing of the sequence in eukaryotic cells. However, applicant is not enabled for inserting any intron into a sequence encoding any polymerase or any gene product with a predictable effect of capability of producing more than one copy of a sequence in a eukaryotic cell while being incapable of being expressed in a prokaryotic cell. The cited references are not enabling for a method of inserting any intron into any polymerase or gene product with the instantly recited outcomes. Mayeda and Oshima (previously cited by applicant) teach that determinants essential for splicing is localized in the intron itself plus 3 nt of the 5' exon rather than the overall structure of the pre-mRNA. This does not mean that the structure of the pre-mRNA is not important to the slicing process, just that the 3 nt of the 5' exon were more essential. Furthermore, Mayeda and Oshima are considered evidence that determinants/structure of the intron itself is crucial to the process, this supporting that not necessarily any intron would result in the instant outcomes when inserted into a nucleic acid encoding any gene product or polymerase. Furthermore, the 3 nt of the 5' exon were crucial for splicing,

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wherein instant claim 245, for example, embraces insertion anywhere in any sequence encoding any polymerase with the instantly recited outcomes. Although applicant argues that intron sequences inserted into a target gene at (C/A) AGG sites are likely to be spliced out, instant claim 245, for example, does not require this. Furthermore, Balvay et al. (previously cited) is evidence that the target structure does in fact play a role in splicing.

Although it is agreed that the issues of unpredictability due to secondary structure as taught by Balvay et al. could possibly be overcome by *in vivo* experimentation, Balvay et al. is evidence that there are additional considerations such as secondary structure that would lead to unpredictability. The instantly recited constructs have extremely broad structural characteristics that were not enabled by the instant specification or the state of the art at the time of filing. Although applicant asserts that Balvay is directed to special occasions, a conclusion of lack of enablement means that, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation (see MPEP 2164.01(a)).

Although applicant argues that Balvay teaches rare circumstances, Jaillon et al. (Nature, Vol. 451, 2008, pages 359-363) teach that most eukaryotic genes are interrupted by non-coding introns that must be accurately removed from pre-messenger RNAs to produce translatable mRNAs and that the mechanisms specifying the correct sites remain poorly understood. Jaillon et al. teach that short introns recognized by the intron definition mechanism cannot be efficiently predicted solely on the basis of

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sequence motifs. Jaillon et al. teach that the intrinsic efficiency of splicing varies widely among introns (see abstract).

Applicants specifically claim that the inserted and inactivating intronic sequences will be spliced out, a process the specification indicates will be carried out by the cellular machinery that normally operates to splice introns out of pre-mRNA sequences. Applicants indicate that such splicing restores native activity to previously inactive proteins. However, the specification as filed does not provide any nucleic acid constructs for which this has actually been shown to demonstrate the predictability of such a broad mechanism. Applicant's specification does not provide sufficient guidance or examples that would enable a skilled artisan to make the disclosed nucleic acid constructs containing sequences that are spliced out by cellular machinery without undue experimentation. Although the specification prophetically considers and discloses making and using such constructs, such a disclosure would not be considered enabling since introducing intervening sequences into nucleic acids alters their secondary structure, which makes their ability to be cleaved by the splicing machinery unpredictable. Applicants have simply not shown that such intervening sequences can be spliced out to restore any activity to previously inactive polymerases (or any toxic protein for that matter).

It is noted that introns can be inserted into genes to control the expression of the gene, as evidenced by the state of the art; (including Gattermann; and Yoshimatsu and Nagawa et al., as cited by applicant). However, none of the references are enabling for a broad method of inserting any intron into any position of any sequence encoding any

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gene product wherein the resultant eukaryotic sequence would express more than one copy of a sequence. None of these references enable the instant genus of predictable splicing of any intron inserted at any position within a sequence encoding any polymerase or gene product.

Again, the issue is not whether it was known in the art how to insert introns, but rather how to insert introns in a predictable fashion in accordance with the breadth of the instant claims and have the desired outcome specific to eukaryotic and prokaryotic cells with regards to any polymerase, as recited in the instant claims. Balvay et al. is simply an example that secondary structure is one complexity when considering splicing mechanisms. The instant claims embrace insertion into locations such as those taught by Balvay.

Applicant argues that inoperative embodiments are permissible because a skilled artisan could determine which embodiments would be inoperative. However, this is not true in the instant case. The skilled artisan would need to practice undue experimentation to determine which embodiments within the instant broad genus are in fact operative as claimed.

In particular, it is demonstrated that the complex secondary structures of nucleic acids are responsible for their intron excision activity, and furthermore, that predicting the ability of the cellular splicing machinery to splice out precise intervening sequences from disrupted sequences with variable secondary structures such that native activity is restored is considered unpredictable, because the splicing machinery is sensitive to the presence or absence of such structures.



Furthermore, the replacement of even a few nucleotides on an mRNA can abolish all activity of the translated protein. It is maintained that neither the specification nor the prior art arms one of skill with the information necessary to engineer sequences into nucleic acid constructs that will be reliably spliced out to result in a protein with native activity restored.

In the absence of sufficient guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

The instant specification at page 85, last paragraph, sets forth that it is possible that insertion of a heterologous processing element may not in all cases inactivate a gene when present in an incompatible cell and therefore supports the unpredictability of the instantly claimed breadth. The specification further sets forth that introns from eukaryotic genes have been introduced into prokaryotic genes with the result of an altered protein.

### ***Double Patenting***

Claims 245, 247-255, 262, 265, 270, and 271 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of copending Application No. 11/929,055. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of application '055 are directed to a construct comprising a nucleic acid encoding a polymerase and a non-native intron sequence wherein the polymerase is incapable of

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being expressed in a prokaryotic cell and is capable of producing more than one copy of a nucleic acid in a eukaryotic cell, which are each elements of the instant claims.

Furthermore, each of the additional elements of the instant claims are embodiments of the '055 claims, as supported by the specification of application '055.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant sets forth that this rejection will be addressed once there is indication of allowable subject matter.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 245, 247-255, 262, 265, 270, and 271 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. (Gene, 127, 1993, pages 233-236), in view of Mount (Nucleic Acids Research, Vol. 10, No. 2, 1982, pages 459-472), and Deuschle et al. (Proc. Natl. Acad. Sci., Cell Biology, Vol. 86, 1989, pages 5400-5404).

The references are of record.

Schwartz et al. teaches introduction of an intron from a hamster gene into a neo gene such that splicing of the neo gene mRNA results in the synthesis of active aminoglycoside phosphotransferase. The unspliced construct is inactive in E. coli, but confers resistance to G418 when tranfected into mouse and hamster cells. Schwartz et al. is evidence that it was known in the art to utilize the insertion of introns to control expression of a gene product in prokaryotic versus eukaryotic cells.

Schwartz et al. do not teach the system specific to a polymerase, and do not teach (C/A)AG sites.

Mount teaches splice junction sequences such as (C/A)AG and teach that the sequences have a possible role as signals for processing.

Deuschle et al. teach the development of a highly regulated expression system in mammalian cells in which transcription of a foreign gene is mediated by the bacteriophage T3 RNA polymerase under the control of the E. coli lac repressor. Deuschle et al. teach that a specific transcription activity can be regulated over a range of several orders of magnitude in higher eukaryotic cells.

The concept of utilizing the insertion of introns to control expression of a gene product in prokaryotic versus eukaryotic cells is taught by Schwartz et al. Although Schwartz is silent as to (C/A)AG sites, it would have been obvious and well within the technical grasp of a skilled artisan to insert the intron next to such a site given that these sequences were known in the art to be present at splice junction sites, which are crucial sites to the splicing of such intron sequences.

It would have been obvious to insert the intron into a sequence encoding a polymerase given that it was known in the art that bacteriophage T3 RNA polymerases are crucial in gene expression systems that regulate genes in eukaryotic cells. One would have been motivated to do so in order to attempt to control the expression of the polymerase in prokaryotic/eukaryotic cells since Shwartz et al. teaches that introns can be inserted to control differential expression.

It would have been obvious to design a nucleic acid construct under the control of intron insertion to control the expression of a gene in eukaryotic vs. prokaryotic cells, wherein the gene product is lethal given that many gene products are disease causing

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or lethal and one would have been motivated to utilize a technology known to control genes differentially between eukaryotic and prokaryotic cells to achieve effective gene expression regulation.

It would have been obvious to utilize a splice junction, which are known to be crucial sites to the splicing of such intron sequences as a matter of design choice given that it was known that (C/A)AG sites are present at splice junction sites, which are crucial sites to the splicing of such intron sequences. Schwartz et al. utilizes insertion of introns to control gene expression in prokaryotes and eukaryotic cells. The difference in splicing mechanisms between the two types of cells was known. It would have been obvious to insert the intron at a site known in the art to be present at splice junction sites that are important to the splicing and therefore control of the intron.

Primer selection as well as insertion of the intron at a known splice site sequence is considered within the realm of routine optimization, as these are elements that were routinely utilized in the art in gene expression control systems.

One would reasonably expect for insertion of an intron of Schwartz et al. at a known splice site or insertion into a sequence encoding for bacteriophage T3 RNA polymerases to result in expression in a eukaryotic cell without expression in a prokaryotic cell.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant argues that Schwartz does not offer motivation to prevent expression of the polymerase in prokaryotes. In fact, Schwartz et al. demonstrate controlling expression in eukaryotes and prokaryotes via teaching that an unspliced construct is inactive in E. coli, but confers resistance to G418 when transfected into mouse and hamster cells.

Although applicant argues that the intron of Schwartz include the flanking exon sequences, this is not excluded from claim 245, for example.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 253 and 254 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 253 recites the limitation "said nucleic acid copy" in claim 245. There is insufficient antecedent basis for this limitation in the claim.

Claim 254 recites the limitation "said DNA or RNA nucleic acid copy" in claim 253, which depends from claim 245. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 245, 247-254, 262, and 270 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Instant claim 245 has been amended to require that the polymerase is capable of producing more than one copy of a "transcriptional unit" from the construct when introduced into a eukaryotic cell. From a review of the specification, and particularly at the passages pointed to by applicant, support is not evident.

Paragraph [0254] discloses that the invention includes "a binary biological function in which a single nucleic acid construct bearing at least two operons or transcriptional units non-native to a cell when introduced into said cell results in the protein gene product of one of the operons impacting the protein gene product(s)", which is not commensurate in scope to the instant claim language. It is not clear what is intended to be embraced by the instant claim, which requires the ability of producing more than one copy of a "transcriptional unit" (undefined) in a eukaryotic cell.

Furthermore, support is not evident for the amendment to claim 262 requiring for the gene product to be expressed in a eukaryotic cell "without any change in amino acid sequence from the native gene".

MPEP §2163.06 notes:

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If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

A review of the specification does not reveal support for where the claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 4/4/11.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita can be reached on (571) 272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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